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Gene Therapy Clinical Trials Raise Troubling Questions

Gene therapy clinical trials were very much in the year-end news-with the focus mainly on adverse events, including at least one death attributed to one such experimental intervention. These events prompted a flood of responses from federal regulatory officials who are charged with evaluating experimental clinical procedures and safeguarding individuals who participate in such trials. At another level, the researchers developing gene therapies are faced with a flurry of troubling questions about their intensive efforts during the past few years, particularly when critical results seem at cross purposes with the aim of producing safe and effective new treatments for a range of genetic diseases, HIV infections, and many cancers.

The death last September of Jesse Gelsinger, an 18-year-old participant in a gene therapy clinical trial at the University of Pennsylvania, did much to trigger the year-end uproar. His death came while he participated in a phase I clinical trial to evaluate the safety of a genetically engineered adenovirus vector designed to correct the relatively rare, inherited disorder known as ornithine transcarbamylase (OTC) deficiency. This disorder disrupts nitrogen metabolism-in severe cases, fatally. Gelsinger's relatively mild OTC deficiency was controlled by a special diet low in protein and medicines that sequester and excrete excess ammonia. Despite the unexpected death, Gelsinger's father and other parents whose children suffer from this or similar metabolic conditions continue to plead with federal authorities not to stop developing or testing such gene therapies.

The University of Pennsylvania clinical trial is one among several hundred gene transfer and gene therapy clinical procedures now under way, mainly at university-based hospitals throughout the country. Proposals for such testing are reviewed by officials at the Food and Drug Administration (FDA) and also are subject to oversight by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) and officials in the NIH Office of Biotechnology Activities (formerly, Office of Recombinant DNA Activities). Although members of RAC once reviewed each proposal, several years ago former NIH Director Harold Varmus

halted that practice and redirected the committee's attentions toward examining broader, gene therapy-related issues.

In December, members of RAC, outside experts, NIH and FDA officials, and members of the news media and public gathered at a meeting on the NIH campus to review both clinical and preclinical findings that speak to the safety of gene transfer and therapy procedures in general and that could address some of the specific questions raised by Gelsinger's death during the University of Pennsylvania clinical trial. The meeting also provided a forum for airing renewed concerns about the effectiveness of federal oversight for such research, whose duties are still shared, albeit somewhat uneasily, by FDA and NIH. In general, officials say they are continuing to improve procedures for sharing critical information, but agreements over how such information should be made public are proving more difficult to forge.

Meanwhile, the scientific and clinical information emanating from the University of Pennsylvania clinical trial and from others that employ adenovirus vectors raises many more questions than it answers.

The genetically engineered adenovirus-based vector developed by James Wilson and his colleagues at the University of Pennsylvania is one among several such vectors now being tested by gene therapy researchers throughout the country. Although those vectors differ in how the viral genes are modified and in what added genes they may carry, most of them now include several gene deletions that render the modified viral particles unable to replicate after they infect mammalian cells. However, because the vectors differ from lab to lab (indeed, the University of Pennsylvania group itself has used several different adenovirus vectors), methods for assessing their potencies vary, and also because patients with widely differing diseases and symptoms are involved in various clinical trials, efforts to judge the overall safety of these vectors are far from straightforward.

The University of Pennsylvania vector, deleted in the E1 and E4 adenovirus genes, was tested extensively in several kinds of mice and primates. Some animals that were tested at high doses developed medical complications, including blood clotting abnormalities and mild to moderate liver damage, and several animals died. It was also administered to about 20 individuals in the University of Pennsylvania OTC clinical trial, several of whom developed varied but, again, moderate adverse symptoms.

That overall experience provided little or no warning of the complications that proved fatal to Gelsinger. Members of the University of Pennsylvania team now attribute his death to an acute respiratory system collapse and subsequent multiorgan failure, perhaps brought on by a massive immune system response. Other unusual findings included severe damage to blood progenitor cells in

the bone marrow, which some experts say suggests a superimposed parvovirus infection.

Wilson and other researchers working with adenoviruses and vectors based on them report additional complicating factors. For instance, the doses at which there are toxic effects or potential therapeutic effects may be separated only narrowly, and there may be abrupt thresholds where adverse effects appear-complicating how vectors might be used and sometimes detracting from the reliability of results from tests in animals. Moreover, depending on specific mutations such viruses contain, they can severely disrupt cytokine-determined inflammatory responses, says Linda Gooding of Emory University in Atlanta, Ga., who served on a NIH-FDA working group reviewing adenovirus-related adverse effects.

Adenovirus vectors also seem erratic in terms of delivering the potentially therapeutic genes they are carrying to intended target cells. For instance, although the University of Pennsylvania vector was applied through a catheter onto the liver of those enrolled in the OTC clinical trial, it apparently distributes widely through other organs and also, at least early on, into immune system cells, based on the Gelsinger case, according to Wilson. Again, the vector acted very differently in the clinical trial compared to how it performed in animal experiments.

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